## SUPPLEMENTAL MATERIALS FOR:

Real-world effects of second-generation versus earlier intermediate/basal insulin analogues on rates of hypoglycemia in adults with type 1 and 2 diabetes (iNPHORM, US)

## AUTHORS

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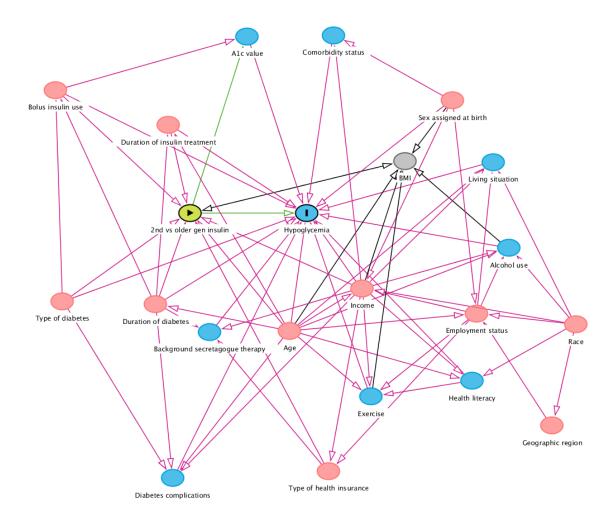
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Supplementary Figure 1: Directed acyclic graph (DAG)\* for the relationship between second-generation compared to earlier intermediate/basal insulin analogue use and hypoglycemia



\*DAG produced using dagitty plotting tool.

	Non-severe hypoglycemia			Severe hypoglycemia		
	Overall	Daytime	Nocturnal	Overall	Daytime	Nocturnal
Intercept	43.56 (28.49 to 66.61)	29.93 (19.3 to 46.43)	13.41 (7.95 to 22.61)	44.5 (23.37 to 84.73)	28.74 (14.06 to 58.74)	18.65 (7.27 to 47.85)
Intermediate/basal insulin						
analogue type						
Earlier	Reference	Reference	Reference	Reference	Reference	Reference
Second-generation	0.81 (0.68 to 0.97)	0.91 (0.76 to 1.1)	0.57 (0.44 to 0.74)	0.87 (0.65 to 1.16)	0.98 (0.71 to 1.36)	0.56 (0.35 to 0.9)
Background secretagogue therapy						
No	Reference	Reference	Reference	Reference	Reference	Reference
Yes	1.42 (1.20 to 1.68)	1.29 (1.07 to 1.55)	1.77 (1.4 to 2.24)	3.05 (2.3 to 4.04)	3.3 (2.39 to 4.54)	2.6 (1.71 to 3.96)
Diabetes type						
Type 1	Reference 0.27 (0.2 to	Reference	Reference	Reference	Reference	Reference
Type 2	0.37)	0.3 (0.22 to 0.41)	0.21 (0.15 to 0.3)	1.22 (0.8 to 1.86)	1.26 (0.79 to 2)	1.38 (0.74 to 2.55)
Duration of diabetes (years)	0.99 (0.98 to 1.01)	1 (0.98 to 1.01)	0.98 (0.97 to 1)	0.94 (0.91 to 0.96)	0.92 (0.89 to 0.95)	0.96 (0.92 to 1)
Duration of insulin treatment (years)	1 (0.98 to 1.01)	1 (0.98 to 1.02)	1 (0.98 to 1.02)	1.05 (1.02 to 1.08)	1.06 (1.03 to 1.1)	1.03 (0.98 to 1.07)
Age (years)	0.99 (0.98 to 1)	0.99 (0.98 to 1)	1 (0.99 to 1.01)	0.95 (0.94 to 0.96)	0.95 (0.93 to 0.96)	0.96 (0.94 to 0.97)
Employment Full-time	Reference	Reference	Reference	Reference	Reference	Reference

Supplementary Table 1: Adjusted rate ratios (95% CI) of hypoglycemia for all estimated parameters, by severity and timing

Part-time	1.95 (1.38 to	2.24 (1.57 to	1.66 (1.08 to	0.47 (0.27 to	0.49 (0.26 to	0.39 (0.18 to
	2.77)	3.21)	2.55)	0.83)	0.95)	0.85)
Unemployed, student, or	1.65 (1.31 to	1.79 (1.41 to	1.47 (1.1 to	0.75 (0.54 to	1.02 (0.72 to	0.39 (0.25 to
retired	2.08)	2.29)	1.97)	1.03)	1.46)	0.62)
Household income (per	1.04 (1.01 to	1.05 (1.02 to	1.02 (0.98 to	0.85 (0.8 to	0.86 (0.8 to	0.8 (0.73 to
\$15,000 increase)	1.08)	1.09)	1.07)	0.91)	0.92)	0.88)
Bolus insulin use	1.43 (1.25 to	1.33 (1.16 to	1.72 (1.42 to	1.97 (1.5 to	1.97 (1.44 to	2.32 (1.55 to
	1.63)	1.54)	2.08)	2.59)	2.68)	3.47)

Adjusted rate ratios were determined by exponentiating beta coefficients estimated by negative binomial regression using generalized estimating equations.

CI: confidence interval.

Supplementary Table 2: Adjusted hypoglycemia rate ratios comparing second-generation to earlier intermediate/basal insulin analogue use among participants who did not change intermediate/basal insulin analogue type during follow-up, by event severity and timing

Type of hypoglycemia	Adjusted rate ratio	(95% CI)
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	All participants (n=413)	Participants who did not change intermediate/basal		
		insulin analogue type (n=385)		
Non-severe				
Overall	0.81 (0.68 to 0.97)*	0.80 (0.64 to 1.01)		
Daytime	0.91 (0.76 to 1.10)	0.90 (0.71 to 1.14)		
Nocturnal	0.57 (0.44 to 0.74)*	0.58 (0.43 to 0.80)*		
Severe				
Overall	0.87 (0.65 to 1.16)	0.80 (0.57 to 1.13)		
Daytime	0.98 (0.71 to 1.36)	0.90 (0.62 to 1.28)		
Nocturnal	0.56 (0.35 to 0.90)*	0.53 (0.30 to 0.93)*		

\*Statistically significant based on an  $\alpha$ =0.05 significance level.

Population-average adjusted rate ratios were determined by exponentiating beta coefficients estimated by negative binomial regression using generalized estimating equations, adjusted for age, employment status, household income, diabetes type, diabetes duration, insulin treatment duration, insulin therapy duration, bolus insulin use, and background secretagogue therapy.

CI: confidence interval.